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Synthesis of *N*-Allylideneamines and Their Use for the Double Nucleophilic Addition of Ketene Silyl (Thio)acetals and Trimethylsilyl Cyanide

Isao Mizota, Yuri Matsuda, Iwao Hachiya, and Makoto Shimizu*

Department of Chemistry for Materials, Graduate School of Engineering, Mie University, Tsu, Mie 514-8507, Japan

mshimizu@chem.mie-u.ac.jp

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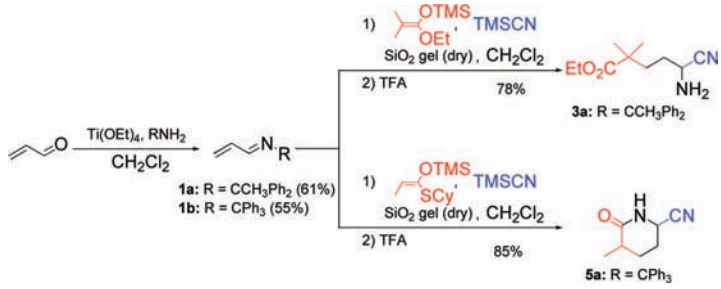
ABSTRACT



***N*-Allylideneamines 1a,b were prepared from acrolein and diphenylethyl or trityl amine in the presence of $Ti(OEt)_4$. Double nucleophilic addition of various ketene silyl (thio)acetals and trimethylsilyl cyanide to these imines proceeded efficiently to give, after workup with TFA, homoglutamic acid derivatives 3 and valerolactam 5.**

N-Allylideneamines **1** derived from acrolein are expected to be important intermediates for the preparation of amino acid derivatives, when these imines **1** are used as acceptors of nucleophiles in a 1,4- and 1,2-double nucleophilic addition. However, difficulties have been always reported for their syntheses, and therefore, there are only a few reports available for the synthesis of this type of imines **1**.[1] Colvin and co-workers prepared a variety of *N*-silylimines for β-lactam synthesis. Although the *N*-allylideneamine **1** protected with a TBS group at the nitrogen was synthesized as one of the examples, it was not used for further reactions.[1d,2] The imine having an electron-withdrawing substituent at the nitrogen was prepared from acrolein[1a] but did not work as an effective acceptor in a 1,4- and 1,2-nucleophilic addition.[3] Yamamoto reported another example, where the formation of this particular imine was only confirmed by GC analysis.[1c] Since there is no substituent at the β-position, the imine **1** has high reactivity and readily undergoes polymerization, which calls for a tedious isolation process.[1]

We have introduced a double-nucleophilic addition reaction of α,β-unsaturated imines with several nucleophiles such as ketene silyl acetals, trimethylsilyl cyanide, trimethylsilyl

(1) (a) Davis, F. A.; Deng, J. *Org. Lett.* **2005**, *7*, 621. (b) Bachrach, S. M.; Liu, M. *J. Org. Chem.* **1992**, *57*, 6736. (c) Uyehara, T.; Chiba, N.; Suzuki, I.; Yamamoto, Y. *Tetrahedron Lett.* **1991**, *32*, 4371. (d) Colvin, E. W.; Mcgarry, D.; Nugent, M. J. *Tetrahedron* **1988**, *44*, 4157. (e) Bock, H.; Dammel, R. *Chem. Ber.* **1987**, *120*, 1971. (f) Boyd, D. R.; Coulter, P. B.; Hamilton, R.; Thompson, N. T.; Sharma, N. D.; Stubbs, M. E. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2123. (g) Hakiki, A.; Ripoll, J.; Thuillier, A. *Tetrahedron Lett.* **1984**, *25*, 3459. (h) Guillemin, J.; Denis, J. *Angew. Chem.* **1982**, *94*, 715. (i) Earl, R. A.; Vollhardt, K. P. C. *Heterocycles* **1982**, *19*, 265. (j) Arques, A.; Molina, P.; Soler, A. *Synthesis* **1980**, 702. (k) Boyd, D. R.; Hamilton, R.; Thompson, N. T.; Stubbs, M. E. *Tetrahedron Lett.* **1979**, 3201. (l) Tamura, Y.; Matsushima, H.; Minamikawa, J.; Ikeda, M.; Sumoto, K. *Tetrahedron* **1975**, *31*, 3035. (m) Ben-Efraim, D. A. *Tetrahedron* **1973**, *29*, 4111. (n) Levine, R.; Fernelius, W. C. *Chem. Rev.* **1954**, *54*, 449.

(2) Although we examined the 1,4- and 1,2-double nucleophilic addition using the imine **1** *N*-substituted with a TBS group, 1,4- and 1,2-double addition products were not obtained.

(3) When 1,4- and 1,2-double nucleophilic addition was carried out using the α,β-unsaturated imine having an electron-withdrawing group at the nitrogen, a 1,4-addition product was obtained instead of 1,4- and 1,2-adducts.

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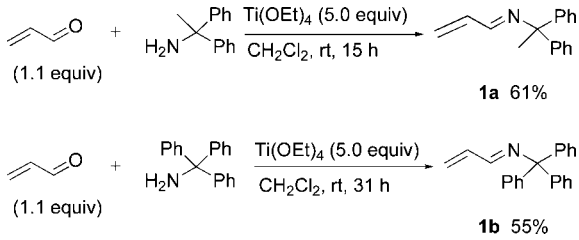
azide, and thiols.[4] A recent result also shows a short synthesis of 2,3,5-trisubstituted pyrroles using these reactions.[4a] We would like to report herein a practical synthesis of *N*-allylideneamines **1a**,**b** and the subsequent double nucleophilic addition reactions with them.

Although we attempted the synthesis of *N*-allylideneamine **1**, e.g., deprotection of the 3-trimethylsilyl-protected imine, oxidation of the allylamines using various oxidants,[5] and condensation of acrolein with amines in the presence of MS 4Å, the imine **1** was not obtained at all. When the condensation of acrolein with the amine was carried out in the presence $Ti(OEt)_4$, the reaction proceeded smoothly to afford *N*-allylideneamine **1a**,**b** having a diphenylethyl or trityl group (Scheme 1).

Scheme 1. Preparation of *N*-Allylideneamines



In order to study the characteristics of these *N*-allylideneamines, we caluculated the LUMO coefficients of the carbonyl (or imino) carbons and β-carbons, which would suggest regioselectivities on the addition of nucleophiles.[6] Based on molecular orbital calculations, electronic and steric effects of the substituent at the imino nitrogen atom should be rationalized (Figure 1).[7]

Structures were fully optimized with HF/6-31G* level using geometry optimization. Calculations were shown to be comparable with the ab initio (HF/STO-3G) method.[8] The values of LUMO coefficients at each reaction site (2- and 4-positions) and the absolute value differences between these coefficients for the optimized geometries are summarized for comparison (Figure 1). Comparison of LUMO coefficients of acrolein and *N*-allylideneamine **1a** gave an estimation of

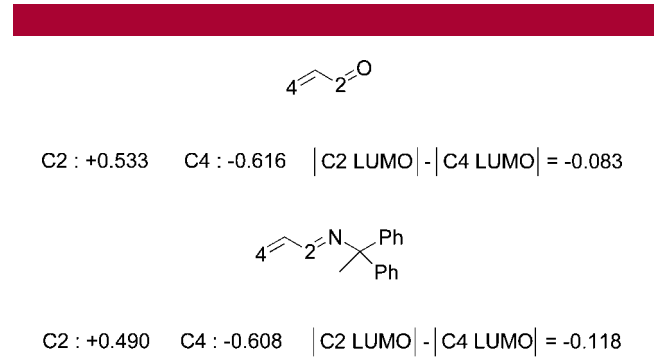
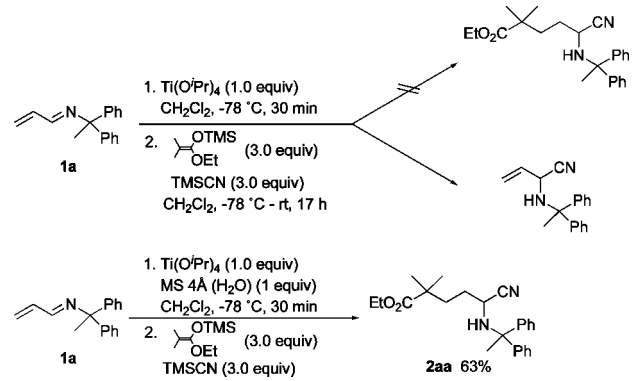


Figure 1. LUMO coefficients of acrolein and *N*-allylideneamine.

regioselectivity for 1,4- and 1,2-addition. Both acrolein and *N*-allylideneamine **1a** have larger coefficients at the 4-position, and the major reaction course based on the HOMO−LUMO interaction would be the 1,4-addition. The involvement of the steric factors suggests that it would be easier for *N*-allylideneamines to be attacked at the 4-position than for acrolein.

We next carried out 1,4- and 1,2-double nucleophilic additions of ketene silyl acetals and trimethylsilyl cyanide to *N*-allylideneamines **1a**,**b**. The *N*-allylideneamines **1b** was decomposed upon treatment with Lewis acids such as $AlCl_3$, $TiCl_4$, and $Ti(O^iPr)_4$. The *N*-allylideneamine **1a** was also decomposed under the influence of $AlCl_3$ and $TiCl_4$. In contrast to the case with **1b**, however, when $Ti(O^iPr)_4$ was used as a Lewis acid, formation of the 1,2-addition product with TMSCN was confirmed by ^1H NMR (Scheme 2). These

Scheme 2. Double Nucleophilic Additions to *N*-Allylideneamine

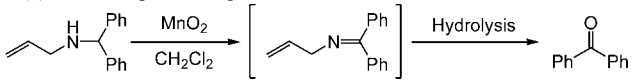


results suggested that use of a weak acid and a proton source would promote the double-nucleophilic addition.[4i] Indeed, the reaction in the presence of $Ti(O^iPr)_4$ and molecular sieves 4Å containing 1 equiv of water gave the desired 1,4- and 1,2-addition product **2aa** in 63% yield.

Among the promoters examined, silica gel was found to be the most effective.[9] The double-nucleophilic addition reactions were next carried out using various ketene silyl acetals under the optimized conditions, and the results are summarized in Table 1. The use of ketene silyl acetals

(4) (a) Shimizu, M.; Takahashi, A.; Kawai, S. *Org. Lett.* **2006**, *8*, 3585. (b) Shimizu, M.; Kamiya, M.; Hachiya, I. *Chem. Lett.* **2005**, *34*, 1456. (c) Shimizu, M.; Kurokawa, H.; Takahashi, A. *Lett. Org. Chem.* **2004**, *1*, 353. (d) Shimizu, M.; Yamauchi, C.; Ogawa, T. *Chem. Lett.* **2004**, *33*, 606. (e) Shimizu, M.; Nishi, T. *Synlett* **2004**, 889. (f) Shimizu, M.; Nishi, T.; Yamamoto, A. *Synlett* **2003**, 1469. (g) Shimizu, M.; Kamiya, M.; Hachiya, I. *Chem. Lett.* **2003**, *32*, 606. (h) Shimizu, M.; Nishi, T. *Chem. Lett.* **2002**, 46. (i) Shimizu, M.; Ogawa, T.; Nishi, T. *Tetrahedron Lett.* **2001**, *42*, 5463. (j) Shimizu, M.; Morita, A.; Kaga, T. *Tetrahedron Lett.* **1999**, *40*, 8401.

(5) For example, benzophenone was obtained from the reaction below.

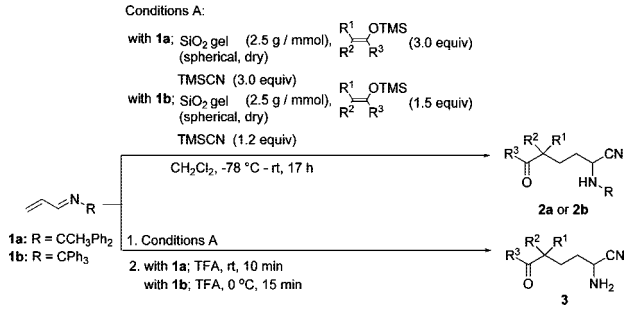


(6) (a) Tomioka, K.; Shioya, Y.; Nagaoka, Y.; Yamada, K. *J. Org. Chem.* **2001**, *66*, 7051. (b) Tomioka, K.; Okamoto, T.; Kanai, M.; Yamataka, H. *Tetrahedron Lett.* **1994**, *35*, 1891.

(7) Calculations were carried out using the SPARTAN pro program and optimization with 6-31G*.

(8) The difference in the method of calculation (HF/STO-3G, and PM3) has little influence on a qualitative conclusion.

Table 1. Examination of 1,4-Nucleophile and Deprotection

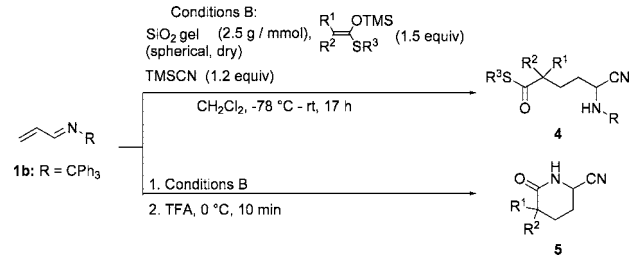


entry	R^1	R^2	R^3	with **1a** **2a**[a] (**3**)[b] (%)	with **1b** **2b**[a] (**3**)[b] (%)
1	Me	Me	OEt	83 (78)	80 (56)
2	Me	Me	OMe	87 (57)[c]	64 (67)
3	Me	Me	O^{n}Pr	− (47)	58 (54)
4	Me	Me	O^{i}Pr	− (27)	68 (59)
5	−(CH$_2$)$_5$−		OMe	87 (76)	59 (61)
6	OEt	OEt	OEt	− (40)	51 (12)
7	H	H	S^{t}Bu	56	22 (-)[d]
8	Me	Me	O^{t}Bu	-[e]	59 (61)
9	SMe	Me	OEt	-[e]	24[f]
10	H	Me	OEt	-[e]	0
11	H	Me	Ph	-[e]	0

[a] Under the conditions A. [b] Under the conditions A followed by TFA treatment. [c] Formation of the cyclized valerolactam (17%) was observed. [d] Although formation of valerolactam was confirmed by ^{1}H NMR; isolation was not successful. [e] Not examined, see ref 10. [f] dr = 53:47.

derived from ethyl isobutyrate and methyl isobutyrate gave the desired 1,4- and 1,2-adducts **2a** in high yields (entries 1 and 2). Due to the instability of some 1,4- and 1,2-addition products arising from the imine **1a**,[10] the in situ transformation into amino nitrile was next examined. Upon quenching with TFA after double-nucleophilic addition, the reaction gave the amino nitrile **3** in 78% yield (entry 1). Using the in situ hydrolysis, the reaction gave amino nitriles **3** in moderate to high yields (entries 2−6). Use of the ketene silyl acetal derived from isopropyl isobutyrate with the imine **1b** gave amino nitrile **3** in good yield, which contrasts to the result with **1a** (entry 4). Use of ketene silyl thioacetal (KSTA)[4g] also gave the desired 1,4- and 1,2-addition adduct **2a** in 56% yield (entry 7). Further examples using ketene silyl thioacetals are summarized in Table 2.

Table 2. Double Nucleophilic Addition Using Ketene Silyl Thioacetal and Transformation into Valerolactam



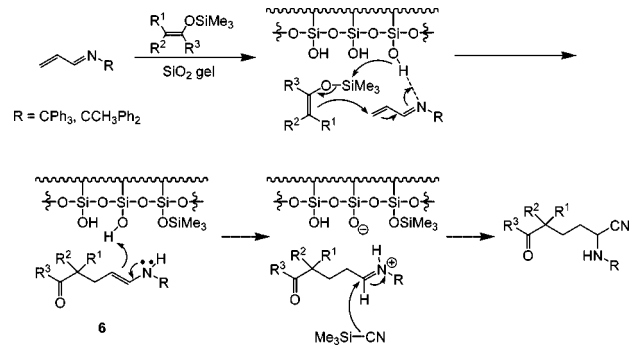
entry	R^1	R^2	R^3	*Z*/*E* (KSTA)	condns B **4** (%) (dr)	condns B/TFA **5** (%) (dr)
1	H	Me	Cy	92/8	75 (50:50)	85 (53:47)
2	H	Me	Et	89/11	69 (71:29)	76[a] (50:50)
3	H	Me	^{t}Bu	94/6	65 (55:45)	71 (47:53)
4	H	Me	^{i}Pr	94/6	68 (58:42)	35[b,c] (66:34)
5	H	Me	Ph	73/27	55[d] (55:45)	64[d] (42:58)
6	H	Me	^{n}Pr	88/12	45 (51:49)	40[c] (46:54)
7	Me	Me	Et	−	39 (−)	53 (−)

[a] Ketene silyl thioacetal (*Z*/*E* = 91/9) was used. [b] Ketene silyl thioacetal (*Z*/*E* = 92/8) was used. [c] Treatment with TFA at rt for 10 min. [d] Reaction time was 24 h.

When the trisubstituted ketene silyl thioacetal derived from *S*-cyclohexyl propanethioate was used under the conditions B/TFA, cyclized valerolactam **5** was obtained in high yield as a result of the good leaving ability of the alkylthio group (entry 1). Valerolactams are often found in various natural products and many of them are of great current interest because of their unique biological activities.[11] The trisubstituted ketene silyl thioacetals studied here gave 1,4- and 1,2-double-nucleophilic addition products **4** or **5** in moderate to good yields (entries 1−6). Use of a tetrasubstituted analogue also gave the product **4** or **5** in moderate yield (entry 7).

A proposed reaction mechanism is shown in Scheme 3. First, the *N*-allylideneamine was activated with silica gel

Scheme 3. Proposed Mechanism



(9) Use of other promoters such as MeOH, PhOH, AcOH, Na_2SO_4·$10H_2O$, Amberlyst 15DRY, and Florisil gave 1,4- and 1,2-addition products **2aa** in low yields. The amount and the shape of silica gel were also examined. See the Supporting Information. Examples using silica gel as a reaction promoter, see: Shimizu, M.; Tanaka, M.; Itoh, T.; Hachiya, I. *Synlett* **2006**, 1687.

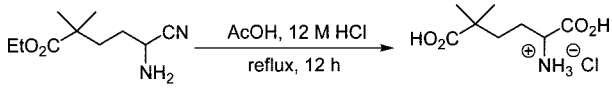
(10) We confirmed by ^{1}H NMR that 1,4−1,2-adduct products **2a** were changed to 1,4-adducts via retro-Strecker reaction (Table 1, entries 3, 4, 6). Since the adducts were not stable, the addition reactions were not examined with **1a** in detail (Table 1, entries 8−11).

(11) (a) Maio, W. A.; Sinishtaj, S.; Posner, G. H. *Org. Lett.* **2007**, *9*, 2673. (b) Taylor, P. J. M.; Bull, S. D.; Andrews, P. C. *Synlett* **2006**, 1347. (c) Bower, J. F.; Svenda, J.; Williams, A. J.; Charmant, J. P. H.; Lawrence, R. M.; Szeto, P.; Gallagher, T. *Org. Lett.* **2004**, *6*, 4727. (d) Lautens, M.; Tayama, E.; Nguyen, D. *Org. Lett.* **2004**, *6*, 345. (e) Cellier, M.; Gelas-Mialhe, Y.; Husson, H.; Perrin, B.; Remuson, R. *Tetrahedron: Asymmetry* **2000**, *11*, 3913. (f) Kobayashi, S.; Akiyama, R.; Moriwaki, M. *Tetrahedron Lett.* **1997**, *38*, 4819. (g) Ezquerra, J.; Pedregal, C. *Tetrahedron Lett.* **1995**, *36*, 3247. (h) Paulvannan, K.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 8197. (i) Bailey, P. D.; Wilson, R. D.; Brown, G. R. *Tetrahedron Lett.* **1989**, *30*, 6781. (j) Angle, S. R.; Arnaiz, D. O. *Tetrahedron Lett.* **1989**, *30*, 515.

followed by 1,4-addition of ketene silyl (thio)acetal to give an intermediary enamine species **6**. Then isomerization to imine was promoted by silica gel followed by 1,2-addition of TMSCN to give the 1,4- and 1,2-product.

Moreover, hydrolysis of the nitrile moiety of amino nitrile **3a** gave amino acid **7** in high yield (Scheme 4).

Scheme 4. Hydrolysis of Amino Nitrile



3a **7** 96%

In conclusion, it was found that the isolation of *N*-allylideneamines having sterically demanding substituents was possible in good yields using $Ti(OEt)_4$. Although the previous double-nucleophilic addition needed strong Lewis acids such as $TiCl_4$ or $AlCl_3$, even the use of silica gel, a weak acid, promoted the double nucleophilic addition to *N*-allylideneamines.[12] Although detailed examination into the scope and limitation of the present reaction is currently under way, amino nitriles and valerolactams are also respectively synthesized using ketene silyl acetals and ketene silyl thioacetals in good yields under the influence of TFA which effects removal of the diphenylethyl and trityl groups. Since weak acids can promote the present addition, this reaction may be used in an asymmetric version with chiral protic acids.

Acknowledgment. This work was supported by Grant-in-Aids for Scientific Research (B) and Priority Areas from MEXT and JSPS.

Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Regioselectivity on the addition of nucleophiles to α,β-unsaturated aldimimes has been studied previously, see ref 4c. Examples using α,β-unsaturated aldimimes for the β-lactam synthesis, see: (a) Fleming, I.; Kilburn, J. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2663. (b) Ha, D.-C.; Hart, D. J.; Yang, T.-K. *J. Am. Chem. Soc.* **1984**, *106*, 4819.